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BELLADONNA AND HYOSCYAMUS.[1]

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PART I.—CULTIVATION EXPERIMENTS.

Atropa Belladonna and various species of *Hyoscyamus* have been carefully studied for some time and descriptions have been prepared by chemical and botanical workers. Recently some additional observations have been made and work done by the writer, the results of which seem of sufficient importance to present.

Seeds of *Atropa Belladonna* L. and of various species and varieties of *Hyoscyamus* were secured from various sources and plants propagated from them used for the work. In the securing of seeds of *H. niger* L. and of *H. albus* L. it was learned that other botanical names were sometimes applied to these plants and that some confusion exists in the use of the various synonyms. According to the Index Kewensis, the following named plants are identical with *Hyoscyamus niger* L.: *H. agrestis* Kit., *H. auriculatus* Tenore, *H. bohemicus* F. W. Schmidt, *H. lethalis* Salisb., *H. officinarum* Crantz, *H. pallidus* Waldstand Kit., *H. persicus* Boiss and Buhse, *H. pictus* Roth., *H. syspirensis* C. Koch, *H. verviensis* Lej., and *H. vulgaris* Neck; and the following identical with *Hyoscyamus albus* L.: *H. aureus* All., *H. canariensis* Ker-gawl., *H. Clusii* G. Don., *H. luridus* Salisb., *H. minor* Mill., *H. major* Mill., and *H. varians* Vis in Flora. Unquestionably there is a wide range of variation in *H. niger* L. and *H. albus* L., and, while some of the above synonyms probably arose from the discovery and naming of the plants by independent workers at about the same time, still others represent

[1] Presented to the Philadelphia College of Pharmacy for the degree of Master in Pharmacy in course.

variations of but a fraction of a unit character from the type. Then again the name *H. agrestis* Kit. has been applied to the specific annual form of *H. niger* L. Many of these early specific names are still more or less in use, and, while one may secure seeds from a number, the resulting plants conform to type specimens of *H. niger* L., *H. albus* L., or to hybrids. Furthermore, it appears to be quite impossible at the present time to secure seeds of Hyoscyamus which represent pure races from any of the various seed dealers.

Culture and Wintering.

The seeds of *H. niger* L. biennial germinate in about the same length of time after being planted as do the seeds of *Atropa Belladonna,* most of the seeds requiring from four to six weeks to come up, while a few may require much longer. The seeds of *H. niger* L. annual and *H. albus* L. germinate quite evenly in from eight to ten days. With proper care the plants make a very rapid growth. No particular difficulty was experienced in the cultivation of several hundred of each species. Hyoscyamus, however, requires rather more attention than most plants in connection with transplanting, spraying, watering, hoeing, etc.

The biennial plants forming the basis of the work reported in this paper were protected during the winters by the following methods: After the first hard freeze coarse straw manure about a foot deep was placed over the garden plots of *Atropa Belladonna* and *H. niger,* the roots of a second lot dug up and buried in a protected location, while a third lot of each were potted and stored in a cold-house. The Belladonna plants all survived the first winter except those left out in the garden plots. During the second winter (1912–13) all Belladonna plants survived. The potted plants of Hyoscyamus were the only Hyoscyamus plants that survived both winters. The lowest outside temperature during the first winter (1911–12), as determined by an accurately recording thermometer placed in the garden, was -33° F., and for the second winter -22° F.

I have subjected the various species and varieties of Hyoscyamus plants and Belladonna plants that I have grown during the past three summers to varying conditions in order to learn more concerning their exact nature and habits. The increased use of drugs from cultivated plants makes such studies of prime importance, and, while

ecologic and physiologic investigations have been carried out with a number of medicinal plants, for the most part these studies have not been made with the object in view of securing vegetable drugs of uniform maximum medicinal values.

The Alternating Annual and Biennial Habit.

In connection with the cultivation of Hyoscyamus I have given some attention to the constancy of the various forms under observa-

FIG. 1.—*Hyoscyamus niger*, biennial. Portion of a plot showing rosette character of the leaves and their long petioles.

tion, to determine the presence or absence of the alternating annual and biennial habit. Before giving the results of my own experiments along this line I will briefly discuss the phenomenon.

De Vries states that in plants which possess the alternating annual and biennial habit the biennial species which presents the character of occurring partly in annual and partly in biennial specimens must possess the capacity of growing as annuals in a semi-latent condition, and that this capacity does not seem to be universal, but to be

confined to particular races. De Vries presents experimental evidence to prove that biennial species which possess this semi-latent capacity are, in becoming annuals, largely influenced by external factors. A large number of plants will become annual if the seeds germinate early or biennial if their seeds germinate late; here the stimulus of the spring frost or cool weather is in some cases a factor which causes annuals or bolting, as in the sugar beet. In addition, many plants possess an inherited variability to be either annuals or biennials.

FIG. 2.—Flowering branches of *Hyoscyámus niger*, annual.

In summing up experiments on Œnothera, De Vries shows that "biennial species which possess in a semi-latent state the capacity to produce annual specimens can be induced to manifest this anomaly to a much greater extent by supplying them with more food. Crowding of plants, shading, lack of manure, or cultivation on sand favors the production of biennials; but the more space, light, and nourishment in the soil there is at the disposal of the individual plants the greater will be the number of those which will produce stems, flower, and ripen their seed the first summer." Continued selection fails to

fix the biennial races and to free them of annual species or to free the annual races of biennial individuals.

Holmes, in considering the occurrence of annual plants in the biennial henbane fields of England, states that "the seeds of the capsules last formed are often deficient in vitality and the plants produced from them flower the first year, hence the occurrence of annual plants among the biennial."

In discussing *Œnothera Lamarkiana* (a plant which possesses the semi-latent alternating annual and biennial habit) De Vries says that he found about the same number of annual and biennial individuals from the upper and lower fruits of the same spike, and, furthermore, he draws the conclusion from his work on *Trifolium pratense quinquefolium* that the better the seeds are fed on the plant the greater is the development of the anomaly on the individuals produced by them. Poor seeds give rise to atavists, good ones to extreme variants.

If we accept the quite general belief that perennial and biennial plants are of older origin than annual plants, then we cannot consider the annual henbane as atavistic. On the choice of seeds in selection De Vries states, after weighing the evidence of a large number of workers, as well as his own, that "when we are dealing with semi-latent or, in general, with highly variable characters a selection of seeds either by their size and weight or by their place of origin on the plant is to be recommended in many cases, and the general rule seems to be that the place of origin of the best seeds will also be that of the desired variants." There are some cases in which this rule does not apply, as in *Trifolium incarnatum*. In this latter plant De Vries found that the reverse of the general rule held good, and the result of this work was so strikingly different from all other that he leaves the explanation an open question. This occurrence of the annual form of *Hyoscyamus niger* in English henbane fields is probably due to hybridization (which will be discussed later in this paper) rather than to semi-latent characters in the biennial Hyoscyamus.

I will now describe my own experimental attempts to bring out semi-latent characters in Hyoscyamus. All plants grown outside were cultivated in the Medicinal Plant Garden, College of Pharmacy, University of Minnesota.

Experimental Planting, 1911.

My first planting, on February 17th, consisted of a sample of seed labeled *Hyoscyamus niger* and purchased as the biennial form. The germination of this sample was very poor, only four seed giving rise to plants. On March 17th three of these plants continued to grow and were transferred from the seed-pan to individual pots. Each plant developed a rosette of basal leaves and was typical of the biennial henbane. All three plants died later in the season, due

Fig. 3.—Flowering branches of *Hyoscyamus albus*.

to lack of attention and a proper understanding of how the plants should be cared for.

A second planting of the seed referred to above was made on March 17th, and in twenty-four days a few seed had germinated. Fifteen plants were secured from this second planting, and these were transferred to a sandy loam plot in the medicinal plant garden as soon as danger of frost was over. The soil or other conditions seemed unsuited for the plants, and they made very little growth after being planted out. A long hot spell resulted in all plants dying. Each plant produced a weak rosette of basal leaves, but there was no tendency for the development of a shoot.

The second sample experimented with in 1911 consisted of a lot of seed purchased as the drug Hyoscyamii Semen. Some of these seed were sown on February 22nd and a second lot on March 26th. Both plantings required about three weeks to germinate. From these plantings seventy plants were secured and transferred to flats containing good, rich potting soil. The plants all made rapid growth and began to send up flowering shoots in about three weeks. The characteristic rosette of basal leaves of the biennial plant was not present in a single specimen. All of the plants flowered before the weather was suitable for outside planting, and, although the plants were small, they represented typical annual *Hyoscyamus niger.*

On April 26th seed of *Hyoscyamus niger, H. albus,* and *H. pictus* were sown in cold frames. These all germinated in from eight to ten days, and *H. albus* coming up first. The soil in the seed beds was very light and sandy. No fertilizer whatever was applied. All of these plants were allowed to remain in the cold frames, the sash being permanently removed as soon as danger of frost was over. The plants were crowded in rows, and the rows were close together. Other larger growing plants around the cold frames soon placed the Hyoscyamus in quite dense shade. The conditions affecting the growth of the plants throughout the season were such, that had semi-latent biennial characters been present in any of the plants one would have looked for a large number of biennial forms. The result of the experiment, however, was that every one of about two hundred plants in each row sent up the flower stalk, produced flowers, and fruited.

Experimental Planting, 1912.

The first planting in 1912 was done on March 2nd, and consisted of three lots of seed freshly imported from Germany and labeled as *Hyoscyamus niger, H. albus,* and *H. pictus.* I secured a good, even germination from each of these trials in two weeks' time. About seventy-five plants of each lot were transferred to flats the 1st of April, and to three-inch pots May 14th. Two weeks later they were planted out in the open garden, being placed in plots of two different kinds of soil. One-half of the three species were placed in a very light sandy loam and the other half in soil consisting of light sandy loam mixed with about equal parts of rich, well-rotted peat and other humus. All of the plants made a good, continual growth from the time the seeds germinated until maturity,

and all plants produced flower stalks, flowers, and fruits without showing any signs of the biennial character.

The second planting for this season was made on March 14th, and consisted of a sample of seed labeled Henbane and purchased for the biennial form. This sample germinated unevenly, but a fairly large proportion of the seed had started to grow by April 10th. About fifty of the plants grown from this lot of seed were placed in flats on April 24th, and the latter part of May they were transferred to the open, twenty-five of the plants being placed in a sandy loam mixed with an equal amount of peat humus, and the remaining twenty-five in a plot the soil of which consisted of about one foot of clean sandy loam underlaid with cinders and sand. All of the plants made a good growth and were all characterized by the numerous typical basal leaves of the biennial henbane. The plants were watered by city water with a hose when rain was not sufficient. Most of the plants in the sand underlaid with cinders died during the latter part of the summer, when it was exceedingly hot. Those plants in the richer soil, however, continued to grow luxuriantly, and by fall many of them were two feet across. None of the plants under either condition showed any sign of producing flower stalks.

The third planting, on March 21st, 1912, consisted of a fresh sample of seed labeled *Hyoscyamus niger* and obtained from Germany. In this planting germination was very poor, only eighteen plants being obtained, and the seed which produced these few plants required from three to four weeks to germinate. All of these plants grew rapidly, produced flowers and fruits, but did not show the biennial habit in any respect, although they were not grown under the most favorable conditions.

Experimental Planting, 1913.

All planting of Hyoscyamus seed in the spring of 1913 was done on February 7th, at which time five different lots of seed were sown.

Lot number one and lot number two were each bought for *Hyoscyamus niger,* biennial. The seed of these two lots germinated quite evenly, requiring from four to five weeks to come up. Twenty plants from each lot were placed in separate flats with rich potting soil on March 20th, where they continued to grow for about three

weeks. The plants were then put into three-inch pots, where they were held until transferred to the garden, early in May. All of the plants were placed in a plot in which the soil was composed of very rich garden loam. A late spring frost injured many of the plants, but they soon recovered and made a vigorous growth throughout the summer. Each plant produced a large rosette of basal leaves, but not a single plant showed any tendency to develop the flowering stalk.

The third, fourth, and fifth lots of seed sown in the spring of

FIG. 4.—Flowers of *Hyoscyamus niger*, annual.

1913 were freshly imported from Germany and were labeled respectively as follows: *Hyoscyamus niger, H. albus,* and *H. pictus.* In each lot germination took place in about ten days. Seventy-five to ninety plants from each lot were transferred to flats as soon as the second pair of leaves were well formed. When the plants became crowded in the flats they were placed into three-inch pots. The plants grew rapidly and many had produced flowers by the time they were planted in the garden, which was early in May. Most of the plants were placed in pots in which the soil was quite rich, and

within a short time every plant had produced a flower stalk, flowers, and fruit. The plants continued flowering throughout the early summer and then died.

The results of these experiments, in so far as semi-latent characters are concerned, may be summarized in a very few lines. Altogether over twelve hundred plants were grown, and these were subjected to a number of varying conditions, with the result that not a single plant showed any tendency to change from the annual to the biennial form or from the biennial to the annual form. While these experiments are probably not conclusive, they indicate that pure races probably exist of the annual and biennial forms of Hyoscyamus.

Hybridization.

The work which I have thus far done has not included any experimental crossing of the different species and varieties of Hyoscyamus, but in the attempt to secure pure species and races for later work some observations have been made which seem worthy of mention. Throughout the cultivation of Hyoscyamus it has been noted that the amount of pigment in the flowers was exceedingly variable. In Hyoscyamus there are two distinct color units, which may be termed physiologic units. The first of these is represented by anthocyanin, to which is due the dark coloring of the veins of *Hyoscyamus niger,* and the second is a yellow element. During the past season, when several hundred plants of Hyoscyamus, grown from commercial seed supplies, were under cultivation, I arranged twenty plants, each with a slightly varying amount of color, in such an order as to represent at the one end a typical specimen of *H. niger* with the maximum amount of anthocyanin, while at the other end of the row a plant difficult, if not impossible, to distinguish from typical *H. albus.* This condition appears to be explained by the somewhat extended experiments on the hybridization of different species and forms of Hyoscyamus by De Vries and by C. Correns. From the results of these experiments it is shown that *H. niger* var. annual readily crosses with *H. albus,* and that the anthocyanin is a dominant character. Crosses between *H. niger* annual and *H. niger* biennial have also been made, and in such crosses the biennial form appears to dominate. The pedigree of the crosses conforms to the laws of Mendel, even when the experiments have been carried into the third generation.

Pollination in Hyoscyamus plants not under experimental control takes place partly by means of insects carrying pollen from the flowers of one lot of plants to the flowers of other plants which may be of a different variety or form. This gives rise to vicinists, and hence seed supplies from field-grown or wild plants collected where several forms are growing together will not infrequently produce hybrids rather than pure species or varieties. And for the same reason commercial seed supplies, unless obtained from plants grown under control or from plants grown in isolated districts, will not

FIG. 5.—Flowers of *Hyoscyamus albus.*

always yield pure races. Furthermore, it should be pointed out that *H. albus* is probably not an elementary species, but rather a retrograde variety of *H. niger,* in which the unit character anthocyanin is more or less latent. This difference between elementary species and certain systematic species has been fully discussed by De Vries, and the importance of a physiological classification based upon physiological units should not be underestimated by those engaged in medicinal plant breeding. To illustrate the difference between an elementary species and a systematic species or variety, De Vries

calls attention to *Datura Tatula* and *Datura Stramonium*, in which every analogy points to the blue as the older and the white as the younger form or retrograde variety. *Atropa Belladonna lutea* is another example of a plant where the physiologic unit anthocyanin is lost or latent, and this plant we consider as a variety of *Atropa Belladonna.* The actual proof of the relationship between elementary species and varieties is, of course, rarely to be obtained.

From this brief discussion on hybridization and the principles involved it seems most probable that the occasional annual forms of Hyoscyamus in the biennial henbane fields of England is due to natural hybridization.

At this time I desire to call attention, first, to the importance of the determination of the exact nature of the plant,—*i.e.*, whether it represents an elementary species, a variety, a hybrid, a constant or an inconstant form; and, second, to the need for close and critical study of the medicinally active constituents as physiologic units. Following this, selection and hybridization for the purpose of producing better drugs may proceed along scientific lines and interchanges or combinations of desired unit-characters formed.

(To be continued.)

STANDARDIZATION OF COMMERCIAL PAPAIN.

By F. W. Heyl, C. R. Caryl, and J. F. Staley.

The term "papain" is supposed to describe an especially prepared product containing the enzymatic constituents in greater proportion, and hence having a higher digestive activity, than the crude juice. Thus, in Merck's "Index" papain is described as having a digestive power on blood fibrin of 1 : 200, whereas the proteolytic activity of the dried juice is only 1 : 80. For the latter determination no method of standardization is suggested, although the fibrin test is probably understood.

The fibrin test is decidedly awkward and inelegant. Furthermore, there are some important disagreements as to the conditions under which the test should be carried out. In Hager's "Handbuch der Pharmaceutischen Praxix" this test[1] is described as being carried out in a medium made slightly alkaline with sodium

[1] Band 1, 640.

hydroxide, and that the fibrin is acted on for from four to five hours at 45° to 50° C. It is there further stated, however, that the products of several different manufacturers vary as to their activity in acid and alkaline medium respectively. Thus it is stated that the preparations of E. Merck and of Gehe & Co. acted best in alkaline medium, while, on the other hand, those of Boehringer and of Finkler were active in acid solution.

The fibrin test has been little used in this country because of the doubtfulness of the method and because of the experimental difficulties involved in carrying it out. During recent years our literature contains several contributions dealing with assay methods which are more serviceable than the assay by means of fibrin.

However, during the period in which these newer methods were being evolved the commercial product has been adulterated to a shameful extent, and the terms "papain" and "pawpaw juice" are not now characteristic of two different products. Indeed, papain now really signifies dried pawpaw juice. We have found no products on the market having a higher digestive strength than has dried pawpaw juice, although the terms "papain," "purified papain," "concentrated active principle," etc., were used in describing some of the various products. Some of these were offered for greatly advanced prices, in one case the price per pound being almost $10. Official recognition of this product, as well as a method for standardization, is very desirable.

Among the newer methods, we have one described by Graber.[2] This method is that of allowing 10 grammes of properly prepared round steak to stand with 0.325 gramme of papain in the presence of 85 c.c. of 0.3 per cent. hydrochloric acid at 52° C. for six hours. The undigested portion should not measure more than 2 c.c. in a graduated settling tube. The proteolytic activity then, under these conditions, is 1 : 30. Graber describes the results obtained by this method in studying the activity of pawpaw juice, but not of commercial papain. He found the proteolytic activity on steak to be greatest in a 0.3 per cent. hydrochloric acid medium.

Horace North[3] examined twelve samples of commercial papain, six of which proved by his method to be inactive. The experimental values showing the comparative activity of the six genuine samples

[2] *Jour. Ind. and Eng. Chem.*, 3, 919 (1911).

[3] Report of Lehn & Fink's Analytical Department, 1910–1912, p. 66.

are not given. North does not state whether or not the active samples contained any starch, although this adulterant was noted by him in the valueless samples. North used the test which is official for pepsin. A residue of 36 c.c. is obtained from ten grammes of coagulated egg-albumin. In the assay 0.05 gramme of papain is allowed to act on ten grammes of albumin. After digestion with a good sample of papain a residue of only 6 c.c. remains. In his calculations North allows for a blank of 1 c.c., exactly as in the U. S. P. method for pepsin. The proteolytic activity then was calculated as follows: There remained 6–1 or 5 c.c. of albumin after the digestion, hence 30 c.c. was digested. The proteolytic ratio, therefore, was $\frac{30}{5}$ or $\frac{6}{1}$. If the papain had digested the 10 grammes completely, the proteolytic ratio would have been 1 : 200. In this case, then, the ratio was 1 : 171. This ratio, like the one given by Graber, is for digestion in an acid medium.

Rippetoe[4] assayed papain by using 40 c.c. of a 0.1 per cent. sodium hydroxide solution, 10 grammes of egg-albumin (prepared as directed in the U. S. P.), and by carrying out the digestion at 52° C. for six hours. The quantity of papain used was 0.1 or 0.2 gramme. The residue left after digestion was transferred to a graduated cylinder and the final volume made up to 70 c.c. The proteolytic activity was indicated by the fact that digestion with 0.1 gramme papain left a residue of 18 c.c., while a blank measured 43 c.c. Other experiments described by Rippetoe show the inhibiting action of hydrochloric acid when present in quantities of 0.2 per cent. or 0.3 per cent.

H. M. Adams[5] again calls attention to the presence of starch, and points out the fact that pepsin may be detected by making a quantitative digestion of beef in the presence of 0.2 per cent. hydrochloric acid. Adam's method of assay is identical with that described by Graber, except that the medium employed is neutral instead of acid. Results are given showing the inhibiting action of 0.3 per cent. hydrochloric acid.

In a recent paper F. F. Shelley[6] has applied a modification of Sörensen's method, and offers a standard for pawpaw juice on the

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[4] *Jour. Ind. and Eng. Chem.*, 4, 517 (1912).
[5] *Jour. Ind. and Eng. Chem.*, 6, 669 (1914).
[6] *Analyst*, 39, 170.

basis of the quantitative formation of carboxyl groups when casein is digested in slightly alkaline solution. R. Delaumay and O. Bailly [7] state that papain is a peptone-forming enzyme. They find that there is no relation between the proteolytic and milk-coagulation powers of papain. They recommend that the method of assay be based on the amount of protein dissolved in unit time.

The work which has been done in this laboratory for the purpose of standardization is based upon the work of Mendel and Blood,[8] and a number of commercial samples have been examined with the methods there given. We will therefore outline the methods used, tabulate our results, and, lastly, state our conclusions at the end of the paper.

Experimental.

The methods other than those used in studying the proteolytic activity were those of the Official Agricultural Chemists.[9] The directions for the protein digestions were as follows:

Preparation of Solutions.—(*a*) Egg-white solution. Separate the whites of six freshly-laid eggs and, after beating slightly, dilute with two volumes of 1 per cent. sodium chloride solution. Mix. Filter through plaited filter paper. Make up to a definite volume [10] and mix thoroughly.

(*b*) Weigh one gramme of the papain and transfer to a dry 100 c.c. graduated flask. Do not make up the solution until everything is ready for the determination. The papain is then taken up with 1 per cent. salt solution, shaken thoroughly, and made exactly to volume. Exactly 30 minutes should elapse from the time the salt solution is poured upon the papain until the aliquots of the solution are taken.

(*c*) N/2 acetic acid.

Determination of Proteolytic Activity at 80° to 100° C.—Into a clean, dry 50 c.c. Erlenmeyer flask place 15 c.c. of standardized egg-white solution, add 1 c.c. of the papain solution and then 9 c.c. of 1 per cent. salt solution. All the digestions are made in a volume of 25 c.c. Transfer at once to the thermostat, already regulated at

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[7] *Bull. Sci. Pharmacology*, 20, 141–7 (1913).

[8] *Jour. Biol. Chem.*, viii, 177 (1910).

[9] *U. S. Dept. Agr. Bur. of Chem. Bull.* 107 (revised).

[10] This solution should be so made that 15 c.c. contains 0.4000 gramme coagulable protein. This requires a preliminary determination and subsequent dilution.

80° C., and allow the digestion to proceed for exactly 15 minutes. Now add 1 c.c. of N/2 acetic acid and transfer immediately to a bath at 100° C. and heat for ten minutes. The time factor should be given the sharpest attention.

Bath at 80° C.—15 minutes.

Transfer—1 minute.

Bath at 100° C.—10 minutes.

In order to faciliate the acidification, a two-holed stopper is used, bearing a long glass tube to serve as a condenser, and a small funnel into which 1 c.c. of acetic acid can be easily placed.

The undigested protein is filtered off on a tared filter paper. Wash free from chlorides. Wash with 10 c.c. of 95 per cent. alcohol, and when this has passed through add 10 c.c. of ether U. S. P. Dry at 100° to 105° to constant weight.

At the same time that the above digestion is carried out, the amount of protein in the egg-white solution coagulable by heat is determined in a blank, *i.e.*, 15 c.c. of the same egg-white solution is mixed with 10 c.c. salt solution (or, better, 9 c.c. salt solution and 1 c.c. of the papain solution in which the enzyme has been destroyed by boiling vigorously for 15 minutes) and the operations are carried out upon this mixture exactly as described above.

Calculate the percentage of protein rendered non-coagulable under these conditions.

Test for Pepsin in Papain.—Take 15 c.c. of the same egg-white solution as prepared for the first digestion. Add 2 c.c. 1 per cent. salt solution, 3 c.c.[11] of N/2 HCl and, lastly, 5 c.c. of a 1 per cent. papain solution. Add 0.5 c.c. toluol to prevent putrefaction. Digest at 40° C. for 15 hours. Add 25 c.c. of a 10 per cent. solution of trichloracetic acid. Heat to boiling on an electric stove. Boil ten minutes and filter through a tared paper, and wash the coagulum free from acid. Wash with alcohol and ether. Dry at 100° to 105° C. to constant weight. At the same time that this digestion is carried out the total amount of coagulable protein present should be determined in a blank experiment.

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[11] For the determination of the proteolytic activity at a concentration of 0.5 per cent. Na_2CO_3, 3 c.c. of a sodium carbonate solution (containing 0.125 gramme Na_2CO_3) was used instead of the N/2 hydrochloric acid. For the determination of the proteolytic activity at the alkalinity of the egg 3 c.c. of salt solution was used.

Calculate the percentage of protein digested under these conditions.

Tryptophane Test No. 1.—5 c.c. of 5 per cent. Witte's peptone in 1 per cent. salt solution, 5 c.c. of 1 per cent. papain extract in 1 per cent. salt solution (toluene, 1 drop). Add 1.2 c.c. 1.71 per cent. HCN solution, and 1.2 c.c. N/10 hydrochloric acid; total volume, 12.4 c.c. Digest in glass-stoppered bottles for 17 hours at 36° to 40° C. Add bromine water drop by drop.

Tryptophane Test No. 2.—5 c.c. of 5 per cent. Witte's peptone digested with 5 c.c. 1 per cent. papain solution and 1 c.c. HCN (1.71 per cent.) at 80° C. for 15 minutes should give a strong tryptophane test with bromine water. Report the intensity of the color in the following comparative terms: Faint, distinct, marked, strong, deep.

Examination of Fictitious Sample.—An apparently fraudulent sample gave the following analytical results: Digestion at 80° C., none; at 36° to 40° C. in 0.2 per cent. hydrochloric acid, 61.0 per cent. and 63.0 per cent.; at 36° to 40° C., at the alkalinity of egg,

TABLE I.

Examination of Samples of Dried Pawpaw Latex Containing no Diluents.

Laboratory No.	3035	3044	3045	3117	3039	3040	3328
Digestion at 80° C., blank.	0.424	0.417	0.417	0.403	0.407	0.407	0.394
Residue	0.174	0.236	0.228	0.169	0.180	0.193	0.165
Per cent. digested	58.9	43.4	45.3	58.1	55.7	52.1	58.1
Digestion at 36° to 40° C.: (*a*) 0.2 per cent. HCl, blank	0.421	0.417	0.434	0.429	0.439	0.434	0.414
Residue	0.433	0.407	0.432	0.421	0.426	0.431	0.424
Per cent. digested	None	2.4	None	1.8	2.9	None	None
(*b*) Alkalinity of egg, blank	0.436	0.417	0.427	0.410	0.425	0.421	0.432
Residue	0.418	0.401	0.406	0.405	0.419	0.423	0.433
Per cent. digested	4.1	3.7	2.6	1.2	1.4	None	None
(*c*) 0.5 per cent. Na_2CO_3, blank	0.435	0.416	0.427	0.410	0.425	0.421	0.414
Residue	0.434	0.432	0.433	0.413	0.430	0.436	0.417
Per cent. digested	None	None	None	None	None	None	None
Tryptophane test, 40° C.	Strong	Deep	Strong	Strong	Strong	Strong	Strong
Tryptophane test, 80° C.	Deep	Marked	Strong	Strong	Marked	Strong	Marked
Nitrogen	9.51	9.87	9.87	9.98	9.59	9.88	9.89
Starch	None	None	None	None	None	None	None
Moisture	6.56	7.13	7.33	7.38	9.21	10.11	13.87
Ash	10.13	11.23	11.12	11.50	9.28	9.62	5.10
Sugars, reducing	None	None	None	None	None	None	None
Sugars, non-reducing	None	None	None	None	None	None	None

TABLE II.

Examination of Papain Samples Containing Starch as a Diluent.

Laboratory No.	3042	961	3077	3034	3043	962	2993	2921	3084	3041	3076	3167	3036	3038	3046
Digestion at 80° C., blank	0.383	0.406	0.421	0.409	0.400	0.406	0.410	0.400	0.413	0.410	0.403	0.383	0.399	0.403	0.403
Residue	0.200	0.200	0.249	0.213	0.253	0.236	0.203	0.237	0.369	0.387	0.311	0.297	0.321	0.376	0.311
Per cent. digested	48.3	50.7	40.8	47.9	36.7	41.4	50.5	40.8	10.7	5.6	20.3	22.4	19.5	6.7	22.8
Digestion at 40° (*a*) 0.2 per cent. HCl, blank	0.441	0.433	0.431	0.424	0.440	0.440	0.401	0.427	0.435	0.424	0.409	0.441	0.396	0.429	0.428
Residue	0.444	0.447	0.436	0.421	0.439	0.427	0.406	0.418	0.428	0.442	0.403	0.441	0.393	0.414	0.431
Per cent. digested	None	None	None	None	None	2.9	None	1.8	1.6	None	1.5	None	None	3.5	None
(*b*) Alkalinity of egg, blank	0.430	0.422	0.431	0.424	0.425	0.427	0.406	0.430	0.434	0.417	0.408	0.435	0.396	0.429	0.428
Residue	0.440	0.407	0.434	0.408	0.425	0.414	0.407	0.415	0.422	0.415	0.405	0.434	0.384	0.414	0.418
Per cent. digested	None	3.5	None	3.8	None	3.0	None	3.5	2.7	None	None	None	3.3	3.5	2.3
(*c*) 0.5 per cent. Na_2CO_3, blank	0.430	0.422	0.447	0.424	0.425	0.427	0.431	0.430	0.429	0.424	0.408	0.435	0.396	0.425	0.428
Residue	0.430	0.421	0.438	0.422	0.439	0.429	0.419	0.433	0.431	0.412	0.412	0.441	0.403	0.416	0.438
Per cent. digested	None	None	2.0	None	None	None	2.7	None	None	2.8	None	None	None	2.1	None
Tryptophane test, 40°	Deep	Marked	Distinct	Strong	Marked	Strong	Strong	Strong	Faint	Trace	Faint	Faint	Faint	None	Strong
Tryptophane test, 80°	Deep	Marked	Marked	Strong	Strong	Faint	Trace	Strong	Faint	Trace	Faint	Faint	Faint	None	Distinct
Nitrogen	7.81	7.52	7.59	7.61	6.20	5.87	7.27	5.44	2.77	2.43	3.97	3.73	2.83	2.14	3.08
Starch	15.12	15.1	18.3	20.11	22.9	20.48	23.71	32.13	43.88	46.22	46.46	52.65	53.51	55.31	57.78
Moisture	8.58	8.35	7.27	8.27	8.63	11.89	8.8	6.07	9.0	9.39	9.25	10.85	9.20	10.94	7.92
Ash	8.62	8.51	7.41	7.87	7.50	6.40	7.29	7.06	1.90	2.30	3.49	2.98	3.76	1.40	3.25
Sugar reducing[1]	None	None	None	None	0.47	None	None	None	7.32	None	None	None	None	3.26	0.75
Sugar non-reducing[2]	None	None	None	Trace	None	None	None	None	11.19	None	None	None	None	None	None
Digestion at 80° C. without added starch (calculated)	56.9	59.7	49.9	59.9	47.6	52.1	66.2	60.1	28.5	10.4	37.9	47.3	41.9	15.0	54.0
Nitrogen (calculated)	9.2	8.9	9.3	9.5	8.05	7.3	9.5	8.0	4.9	4.5	7.4	7.8	6.08	4.7	7.3
Ash (calculated)	10.1	10.0	9.0	9.8	9.7	8.0	9.5	10.4	3.4	4.2	6.5	6.3	8.0	3.1	7.7

[1] As dextrose. [2] As sucrose.

there was no digestion, and the same result was obtained when the digestion was carried out in a medium of 0.5 per cent. Na_2Co_3. It gave negative tryptophane tests under both conditions. Nitrogen,

TABLE III.

Examination of Papain Samples Containing Sugar as Diluent.

Laboratory No	3118	3037	3083
Digestion at 80° C., blank	0.400	0.399	0.421
Residue	0.274	0.298	0.327
Per cent. digested	31.5	25.3	22.3
Digestion at 36° to 40° C.:			
(*a*) 0.2 per cent. HCl, blank	0.422	0.408	0.406
Residue	0.214	0.215	0.216
Per cent. digested	49.3	47.2	47.0
(*b*) Alkalinity of egg, blank	0.428	0.407	0.438
Residue	0.422	0.401	0.435
Per cent. digested	1.4	1.5	None
(*c*) 0.2 per cent. Na_2CO_3, blank	0.428	0.408	0.439
Residue	0.423	0.410	0.440
Per cent. digested	1.0	None	None
Tryptophane test, 40° C.	Distinct	Marked	Distinct
Tryptophane test, 80° C.	Faint	Faint	Faint
Nitrogen	5.79	6.15	5.81
Starch	None	None	None
Moisture	4.14	....	....
Ash	9.95	4.11	4.21
Sugar, reducing [1]	24.75	24.5	25.65

[1] Calculated as lactose.

1.3 per cent. and 1.34 per cent.; starch, none; moisture, 9.59 per cent.; ash, 4.05 per cent. Reducing sugar was determined after inversion with hydrochloric acid, and when calculated as glucose amounted to 73.75 per cent.

SUMMARY.

1. In these digestions with pawpaw juice it has again been shown that the digestion proceeds rapidly at 80° to 100° C. This characteristic property can be utilized for the standardization of commercial papain samples.

2. Under the conditions outlined above, dried pawpaw juice should be capable of dissolving at 80° to 100° C. not less than 40 per cent. of the egg-albumin taken.

3. No samples of "papain" were found upon the market which had a higher digestive activity than the samples of dried pawpaw latex under the conditions employed.

4. Since the use of the term "papain" has given rise to the conditions pointed out in this paper, we are inclined to the view that papain products ought to be marketed as "dried pawpaw juice," and that only a lower limit of digestive strength should be stated in defining a standard for it. A definition proposed upon this basis might be stated as follows: Dried pawpaw juice is the dried albuminous exudate of the fruit of *Carica Papaya*. L. (Fam. Papayaceæ), free from starch, sugars, and diluents, and contains a proteolytic enzyme or enzymes. When assayed by the method above [12] it has the power of digesting at 80° to 100° C. not less than 40 per cent. of the unaltered egg-white protein.

5. Of twenty-six samples studied, seven represented the undiluted dried latex, fifteen contained starch in amounts varying from 15 per cent. to 58 per cent., while three were diluted with sugar and one with dextrin. Four samples showed a high digestive strength under conditions favorable for pepsin digestion. On the basis of the standard proposed above, twelve samples, or 44 per cent., have been diluted to such an extent that their digestive strength is below a very reasonable requirement.

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PURE DRUGS AND THE PUBLIC HEALTH.*

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Food and drug laws are generally recognized as being economic measures designed to prevent dishonest practices or gross adulteration and thereby secure to the purchaser an equitable return and the assurance that the food or drug product purchased will be true to name or nature as represented by the seller. The pure drug features of these laws, however, combined with the laws designed to restrict the practice of pharmacy to specially trained and capable individuals, also have, or should have, an evident bearing on public health in that the purchaser is led to assume that the licensed druggist is directly responsible for the character and purity of the drugs sold.

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[12] See page 545.

* Reprinted from the Public Health Reports, vol. 29, No. 19, May 8, 1914.

The methods adopted for enforcing these laws in the past have not always been in accord with the securing of the best results from a public-health point of view, and even in States where the control of laws regulating the nature and purity of drug products is in the hands of the State board of health the tendency has been to discourage rather than encourage adequate and satisfactory control of all medical supplies.

Some indication of the nature and variability of the products sold as medicine may be had from a comparative study of Hygienic Laboratory bulletins embodying in the form of annual compilations a "Digest of Comments on the Pharmacopœia of the United States and on the National Formulary."

These bulletins, though not compiled especially for this purpose, reflect from year to year the available material regarding published activities of food and drug laboratories so far as they relate to pharmacopœial or official drugs and preparations, and the sum total of the reported activities well indicates the general trend of the trade so far as it is influenced by the present-day method of drug-law enforcement.

A compilation of the analytical reports embodied in previously published bulletins shows that out of a total of more than 9000 samples of 6 pharmacopœial preparations reported on during the years 1907 to 1911, inclusive, more than 4000, or approximately 45 per cent., were found to be not in compliance with the requirements of the Pharmacopœia. That approximately this same ratio still holds is evidenced by the available annual reports of State boards of health and State food and drug commissioners, abstracted in Hygienic Laboratory Bulletin No. 93, embodying a Digest of Comments on the Pharmacopœia of the United States and on the National Formulary for the calendar year ending December 31, 1912. Among the reports reflected in this bulletin we find that the chemist of the Indiana board of health states that of 365 samples of drugs analyzed 156, or 42.7 per cent., were illegal in that they did not comply with the standards or requirements. The food and drug commissioner of South Dakota reports that of 326 samples examined 118, or 36.3 per cent., were not passed, and in New Hampshire of 421 samples of drugs examined by the chemist of the board of health 180, or 42.8 per cent., were not conformable.

Further evidence regarding existing conditions will be found in the accompanying table showing the total number of samples of

26 drugs and preparations reported on during 1912, the number that were rejected or found to be illegal, and the number of reporters on each individual article.

TABLE SHOWING REPORTED RESULTS OF ANALYSIS OF SAMPLES OF 26 OFFICIAL ARTICLES—A COMPILATION OF DATA INCLUDED IN HYGIENIC LABORATORY BULLETIN NO. 93.

	Number of reporters	Number of samples		Per cent. of samples rejected
		Examined	Rejected	
Alcohol	7	98	47	47.9
Ammonia, aromatic spirit of	5	116	78	67.2
Ammonia, water	4	19	11	57.8
Asafœtida	10	256	200	78.1
Belladonna, tincture of	3	14	6	42.8
Camphor, spirit of	19	802	423	52.7
Camphor, liniment of	8	597	99	16.5
Ferric chloride, tincture of	7	680	219	32.2
Ferrous iodide, sirup of	8	549	88	16.0
Ginger, tincture of	9	74	30	40.5
Iodine, tincture of	18	984	474	48.1
Lard	8	265	53	20.0
Lemon extract	10	252	100	39.6
Lime water	10	635	98	15.4
Linseed oil	12	367	138	37.6
Olive oil	13	912	69	7.5
Opium, camphorated tincture of	5	91	30	32.9
Opium, tincture of	11	252	125	49.6
Peppermint, spirit of	14	270	139	51.4
Solution of hydrogen dioxide	13	1,026	90	8.7
Solution of potassium arsenite	7	570	128	22.4
Sulphur	6	70	35	50.0
Sweet spirit of nitre	22	609	336	55.1
Turpentine, oil of	8	639	132	20.6
Vanilla	12	286	116	40.5
Witch hazel	5	91	24	26.3
Total	.....	10,524	3,288	31.2

As an object lesson this table is well worth studying from various points of view. Not the least important in this connection is the suggestion that, despite the apparently large number of samples examined, the present-day method of enforcing food and drugs laws is hopelessly inadequate so far as offering to control, even in a moderate degree, the nature and purity of drug products as they reach the consumer.

The limitations imposed by the present method of enforcing the drug feature of food and drugs laws is well illustrated by a table recently published by L. P. Brown, food and drug commissioner of

Tennessee (*Am. Food J.*, 1912, v. 7, July, p. 9), showing the number of States in which food and drugs laws are actually being enforced, the number of employees in each State, and the number of samples analyzed in one year. This table states that no less than 44 political divisions of the United States makes some attempt to enforce laws of this type. The total number of employees recorded is 465, an average of but 10 to each State. The total number of samples examined during one year is given as 83,498, and from a study of several annual reports it is fair to assume that not more than from 20 to 25 per cent. of these samples represent drug products or products used as drugs.

When one remembers that in the United States alone there are no less than 40,000 retail drug stores, and that each one of these stores has in stock from 1000 to 20,000 separate articles used or offered for use as medicine, the futility of endeavoring to control or even to seriously influence the nature and purity of products sold as medicines by an occasional examination of one or more preparations is at once apparent.

That the present-day method of enforcing food and drugs laws is efficient in some directions must be admitted, and the possibilities in this line are well indicated in the above table. Given a product that is more or less easily examined by chemical means and for which a reasonably high standard has been established by the Pharmacopœia, by statute, or by regulation, little or no difficulty is encountered in materially improving the conditions under which such an article is marketed, and thus securing for the consumer a reasonably reliable product if he will but exercise ordinary care in making his purchases from reputable dealers.

One instance of this type is olive oil, which up to a comparatively few years ago was considered to be among the most adulterated of all commercial products. This oil, though largely, if not preponderatingly, used as a food product, is also of value as a medicine and can now be classed among the generally pure articles used for medicinal purposes.

Another article that has been materially improved through systematic examination and accompanying publicity is "solution of hydrogen peroxide." This preparation is also used quite extensively in the arts as a bleaching material, and formerly it was quite common to find the comparatively impure and usually weak technical product on sale in drug stores for medicinal purposes. Improved methods of manufacture, the use of preservatives, and the exercise

of a little additional care in keeping the preparation have evidently combined to change this preparation from one that was considered to be uniformly impure to one that complies fairly well with the spirit though not the exact letter of the present pharmacopœial requirements. Disregarding the frequent presence of a preservative, only 8.7 per cent. of the preparations examined were found to be deficient in strength or contaminated. This figure, when one considers the unstable nature of the product, compares very favorably, indeed, with the low percentage (7.5 per cent. of samples of olive oil rejected during the same period).

Oil of turpentine is another product that is rapidly being improved, and the economically closely related linseed oil, while still above the general average for all of the products reported on during 1912, also evidences a marked improvement over previously reported conditions. These two products are very widely used for technical purposes and occupy rather an anomalous position as drugs. The frequency with which they are now found to be of inferior quality is no doubt due to the fact that little or no attempt has as yet been made to regulate their identity or purity for technical purposes, and because of the much lower price of the impure technical products they are very frequently sold in place of the official, or pharmacopœial, articles for medicinal use.

The opposite of these rather promising conditions is shown in connection with asafœtida, a drug product of somewhat uncertain value that is, nevertheless, used quite extensively, largely perhaps because of its penetrating odor and disagreeable taste. The pharmacopœial requirements for this drug are unnecessarily high and the chemical tests for identity and purity quite inadequate. It is, therefore, not at all surprising to learn that more than 78 per cent. of the samples of asafœtida examined did not comply with the requirements of the Pharmacopœia.

This drug is, however, but one of a number of articles that are of uncertain medicinal value, are difficult to control from a chemical point of view, and are more frequently found to be below standard than above. This one fact, that there are hundreds of more or less widely used drugs for which we have little or no data on which to base a chemical control of the finished preparation, serves to further illustrate the difficulty of exercising any adequate control of medicinal preparations through a city, State, or Federal laboratory.

That some form of control is essential is evidenced by the head

of one of the leading drug houses in England, who is reported as saying that the thousands of samples of crude drugs examined annually in his laboratories yield abundant evidence to show that constant and efficient control is necessary if the purity of medicinal products is to be maintained and progress achieved on the lines of modern science.

The reports of the several officials intrusted with the enforcement of laws relating to the production and sale of drugs have emphasized time and again that much of the material that is now being sold as medicine in this country is either directly harmful or absolutely useless, and that from a public-health point of view considerable progress is necessary before the consumer is as adequately safeguarded as he should be.

It is generally recognized that once a seal is broken, a package opened, or a cork drawn, the manufacturer can no longer be held responsible for the content of the package, and, quite irrespective of the nature of the medicine, the pharmacist in dispensing a portion of an original package assumes all responsibility for the nature and purity of the article.

That this responsibility of the pharmacist is as yet not appreciated and that much progress must be made in the enforcement of existing laws before the public is as adequately protected as it should be, or has a right to expect, is evidenced by the shortcomings of the pharmaceutical preparations included in the table referred to above, particularly those preparations usually made on a comparatively small scale in the retail drug store. From the point of view of State or national officials, these preparations offer the most serious difficulties in the way of control, through the intervention of Federal or State laboratories, and yet they are of considerable importance from a medical point of view in that they include some of the most widely used medicines we now have. It has been well said that medicine, particularly the use of medicines, as a science can make little or no progress until physicians know more of the nature and composition of the articles they use as medicines and of the action or influence of these articles on the healthy as well as the diseased organisms.

How little actual reliance can be put in the average drug preparation at the present time will be appreciated when we learn that fully 50 per cent. of such widely used articles as aromatic spirit of ammonia, spirit of camphor, tincture of iodine, tincture of opium, spirit

of peppermint, and spirit of nitrous ether have been found to be adulterated or below standard.

Some additional argument for more adequate control of the identity, purity, and strength of materials used as medicine is offered by the table including a compilation of data showing the variability of well-known and widely used drugs which can, in a measure at least, be controlled by assay and analysis. Preparations of these drugs, on assay, are less frequently found to be above than below standard, and even a standardized preparation is far from being permanently so.

TABLE SHOWING VARIATIONS IN THE ACTIVE PRINCIPLES OF DRUGS REPORTED DURING THE CALENDAR YEAR ENDING DECEMBER 31, 1912.

[*A compilation of data included in Hygienic Laboratory Bulletin No. 93.*]

	Number of reporters	Number of samples.	Minimum per cent.	Maximum per cent.	U. S. P. requirements.
Belladonna leaves..	5	144	0.175	0.563	0.3 per cent. mydriatic alkaloids.
Belladonna root...	6	115	.11	.780	0.45 per cent. mydriatic alkaloids.
Guarana.....	3	41	3.720	5.16	3.5 per cent. alkaloidal principles.
Hydrastis.....	8	114	2.3	4.85	2.5 per cent. hydrastine.
Hyoscyamus.....	4	120	.043	.234	0.08 per cent. mydriatic alkaloids.
Ipecac.....	10	253	1.24	2.75	1.75 per cent. ipecac alkaloids.
Jalap.....	6	173	3.67	21.76	7 per cent. total resin.
Stramonium.....	4	127	.14	.470	0.25 per cent. mydriatic alkaloids.

As is well known, all pharmaceutical preparations and many drugs and chemicals deteriorate on keeping, and this deterioration is not so much dependent on time alone as a number of accompanying factors, as light, heat, atmospheric conditions, and the general lack of care or technical knowledge in storing the various substances. All in all, it is safe to assert that no matter how excellent a drug or preparation may be when it leaves the producer there are many possibilities for it to become worthless, if not positively dangerous, through carelessness or neglect before it reaches the consumer.

The general subject of changes produced in a drug because of deterioration due to improper keeping has received altogether too little attention and it is not generally recognized that many of the formerly well known drugs have probably been discredited because of their failure to accomplish the object for which they were administered, a failure perhaps largely due to some form of contamination or to decomposition not recognized by the dispenser.

In addition to the changes in drugs that may be produced by heat,

by the constituents of the air, by ferments, or by microörganisms, some recent observations by Neuberg, of Berlin, suggest that nearly all types of organic compounds acquire a pronounced photosensitiveness when they are mixed with inorganic compounds. Iron salts, it is said, provoke such changes most strikingly, and it is quite possible that otherwise innocuous materials may thus be converted, in part at least, into decidedly harmful compounds.

In addition to this possible deterioration of medicaments, which can be averted, to a considerable degree at least, by constant care and watchfulness, there are a number of other factors that should be taken into consideration in connection with the dispensing of medicines to the consumer. Not the least important of these several factors is the accuracy and also the sensitiveness of scales, weights and measures. On page 43 of Hygienic Laboratory Bulletin No. 93 will be found several references that bear out this assertion. One observer found that not one of 36 graduates examined was correct. Some were better than others, but all were bad. In the State of Kansas nearly one-half of the prescription weights examined were condemned, and of the 718 prescription scales examined 195 were found to be unfit for use.

The inability or unwillingness of retail druggists to assume proper responsibility is further evidenced by the recommendation of one man to use ready-made tablets in place of weighing out small quantities of potent drugs. The fallacy of this advice has more latterly been emphasized by the fact that compressed as well as other tablets, even under most favorable conditions, may vary from 10 to 30 per cent. from the quantities claimed. Under conditions not so favorable even greater variations have been observed, and in cases where tablets have been made to sell at inordinately low prices it has been found that expensive chemicals were present only in traces sufficient to give qualitative tests.

In conclusion it may be reiterated that the more evident shortcoming in the present-day enforcement of pure-drugs laws is the general failure to properly place the responsibility for the nature, kind, and purity of the medicines supplied to the consumer where it belongs. This shortcoming is being corrected, to some extent at least, by recently enacted laws to regulate the practice of pharmacy by placing the responsibility squarely on the person dispensing the drug.

The proper enforcement of laws designed to regulate the practice

of pharmacy in conjunction with pure-drugs laws should relieve physicians and the public of any doubt as to the composition, purity, quality, and strength of all drugs and medicinal preparations used in the treatment of disease. As these laws are enforced at the present time it is plainly evident that the methods of control are inadequate and do not serve to safeguard public health as well as they could or should.

Boards of health and other State and Federal officials intrusted with the enforcement of these laws should endeavor to call attention to the desirability of having druggists exercise a close scrutiny of the drugs and preparations included in their stock, to keep drugs, chemicals, and preparations in suitable containers, to throw away old or useless material, and to see that scales, weights, and measures are reliable and accurate under the conditions imposed upon them.

Some effort should also be made to see that drug stores are equipped with the necessary analytical apparatus with which to analyze or examine all supplies and thus assist in maintaining a more efficient control of the articles sold as medicine.

Consistent and efficient control of the identity, purity, and strength of all drugs and preparations as furnished the consumer would make for progress in the science of medicine and should prove to be an important factor in promoting public health.

PROGRESS IN PHARMACY.

A Quarterly Review of Some of the More Interesting Literature Relating to Pharmacy and Materia Medica.

By M. I. Wilbert, Washington, D. C.

The changes in values of medicinal products of all kinds continue to attract general attention in the drug trade. Stocks of a number of chemicals, as well as many of the foreign botanical drugs, have been practically exhausted, and the prices asked for these substances remain high. In connection with many other drugs, prices have decreased to some extent, and market conditions generally are now fairly well fixed. The values of opium and its alkaloids remain high, as do prices for nearly all drugs and chemicals of German or of Austrian origin. Prices for mercurials of all kinds, Russian paraffin oil, thymol, phenol and phenol products generally

are unusually high, and, because of the scarcity of these products, still have an upward tendency.

In Great Britain the war is bringing about a peculiar condition of affairs which may ultimately have a far-reaching, disturbing influence on patent law enforcement. A recent report (*Pharm. J.*, 1914, vol. 93, p. 569) states that the Board of Trade has granted the application of Mr. S. Wellcome for a license to manufacture and sell in Great Britain the drug salvarsan, or "606." The registration of the trade-mark has been suspended for the time being, and it is proposed that patents for other chemicals of German origin not now worked in Great Britain will also be suspended.

The New British Pharmacopœia was placed on exhibition for review in London on October 1, and will be available to the book trade on December 31, 1914. In general appearance the new Pharmacopœia closely resembles the British Pharmacopœia now official, the size of the two books being approximately the same, despite the 67 additional pages in the new pharmacopœia, the discrepancy being accounted for by the use of somewhat thinner paper. The general impression imparted by the printed page is that the type and arrangement of the material is practically the same.

The several British pharmaceutical journals have presented elaborate reviews of the Pharmacopœia, and one wholesale house, Messrs. Southall Bros. & Barclay, Ltd., of Birmingham, has distributed a pamphlet, of 24 pages of comments on the new Pharmacopœia, so that the available literature on the book is already quite extensive.

From the reviews which have appeared in the several journals it would appear that the deletions from the British Pharmacopœia are chiefly of drugs and preparations, while the additions are mostly long overdue and include 25 chemicals, 24 galenical preparations, and 3 crude drugs.

The alterations in strength are of considerable moment and are being actively discussed in British pharmaceutical journals. The provisions of the Brussels Conference Protocol have generally been followed, special attention being directed to the exceptions made. The proposed international drop counter is recognized, the dropping device being described.

Metric weights and measures only are to be used in making or testing official products; the term "mil" is recognized as a short

official designation to be used in place of the more cumbersome cubic centimetre. Imperial weights and measure appear only in connection with the doses.

The Latin nomenclature employed in the Ph. Brit. V. has much in common with that employed in our own Pharmacopœia of the United States, and a table of abbreviations of Latin names of official drugs and preparations appears in the index. This has been somewhat roughly handled by the British reviewers.

An editorial (*Chem. and Drug.*, 1914, vol. 85, p. 480) says: "It is hoped that the abbreviations included in the Ph. Brit. V. will never be put forward as legally binding. They do not appear to be at present, but the list should not go unnoticed; many of the abbreviations are horrible."

Considerable attention has been devoted to the lead and arsenic limits in a number of chemical substances. Tables reproduced in the British pharmaceutical journals show that limits have been fixed for a total of nearly one hundred official substances.

The number of crude drugs and their preparations which are required to be standardized has been increased, and the methods of assay have been brought up to date.

From the available comments it would appear that the pharmacists of Great Britain are still somewhat dissatisfied with the method of revising the Pharmacopœia, but that the book, despite its many shortcomings, is nevertheless a great improvement over its immediate predecessor.

The publication of the British Pharmacopœia has again revived interest in Great Britain in the subject of local pharmacopœias. In a recent discussion of the subject (*Pharm. J.*, 1914, vol. 93, p. 550) it is pointed out that booklets of this nature are intended for permanent use and that there is no reason why they should not be fashioned after a good model so as to make them not alone useful but also attractive to medical practitioners for whom they are intended.

In our country the failure to enact the *Harrison bill* into law before the adjournment of the second session of the sixty-third Congress was rather widely deplored. Despite the opposition that has been manifested at times, it is generally recognized that the Harrison bill is in no way a regulatory measure, but that it is likely to be of considerable value in this respect because of its being designed to fur-

nish the information necessary to make State and other local regulatory measures operative. The text of the bill as finally agreed upon in the Conference Committee is acceptable to physicians and pharmacists generally, though many believe that it is unnecessarily comprehensive and will entail a greater expenditure of time and money to enforce than is necessary to attain the objects aimed at. In the event that the Conference Report is agreed to by the Senate and the bill is signed by the President, the new law will become operative on March 1, 1915.

Proprietary Remedies.—The report of the Select Committee of the House of Commons on Patent Medicines has been published as a separate volume of 782 pages, and is now available through the book trade at 6s. 7d., or, with the somewhat elaborate index, 7s. 6d. The book contains, in addition to the findings of the committee, a verbatim report of the evidence of 42 witnesses who appeared before the committee at the 33 public sittings held from May 12, 1913, to June 12, 1914. One of the abuses commented on by the Select Committee is the fact that the government, in a way, is a party to fraudulent practices because of the collecting of a stamp duty on " patent " medicines or secret nostrums, which stamp carries with it at least the suggestion of recognition or endorsement by the government.

In this connection pharmacists in this country are to be commended for their activity in opposing the imposition of a stamp tax on patent medicines. Many medical practitioners and pharmacists feel that such a tax would, in a way, be an endorsement of these products and would give them a standing not at all in keeping with our present-day knowledge regarding the possibilities and limitations of drugs and medicines.

Roemer, John, in a general discussion of the patent-medicine problem, expresses the opinion that pernicious nostrums can be consistently divided into six classes:

1. Those that bear false statements.
2. Those whose claims for medicinal virtue are exaggerated.
3. Those that contain narcotics.
4. Those that contain alcohol in disguise as medicine.
5. Those that are exploited for venereal diseases.
6. Those that are exploited by subterfuge as emmenagogues.

Such preparations as may be included in the above classification

can claim no justifiable right of existence, much less sanction or tolerance for sale through legitimate pharmacy.—*Proc. New York Pharm. Assoc.*, 1914, p. 286.

The rapid growth of pharmaceutical manufacture in this country is commented on in an article entitled "Drug Intoxication," published in *Public Health Reports* (October 16, 1914, vol. 29, p. 2767), and the suggestion is made that the steady increase in the death-rate from so-called degenerative diseases may be in a measure accounted for by the injuries brought about by the promiscuous use or abuse of actively poisonous drugs.

Bromide Rash.—Weiss, Ludwig, reports an unusual case of bromoderma of the leg in a female, aged 24, who had taken potassium bromide for a number of years.—*J. Am. M. Assoc.*, 1914, vol. 63, pp. 635–639.

Suicides and Newspaper Publicity. (*Anon.*)—The probable influence of newspaper publicity of details with regard to the nature and kind of substances used in connection with cases of poisoning is well shown by a compilation from the reports of the coroner of St. Louis for the years 1910 to 1914, inclusive. The figures given suggest the desirability of telling the truth in regard to the action of corrosive poisons and the need for refraining from even an intimation that the use of any one poison or substance may lead to a sure and painless death.—*J. Am. M. Assoc.*, 1914, vol. 63, pp. 600, 601.

Poisons and Habit-forming Drugs.—Progress in the way of legislation to restrict the sale and use of poisons and habit-forming drugs is reviewed in the introduction to a second supplement to Public Health Bulletin No. 56. This supplement, the introduction to which appears in *Public Health Reports* for November 13, 1914, includes a digest of laws and regulations relating to the possession, use, sale, and manufacture of poisons and habit-forming drugs enacted during 1913 and 1914. The compilation should be of considerable interest to pharmacists in all parts of the United States who may be called upon to endorse or to oppose prospective legislation along this line.

Solid Alcohol.—The use of solidified alcohol for rubbing and for general disinfection purposes is meeting with increasing popularity. The production of alcohol in solid form would appear to offer a

possibility for denaturing the product in such a way as to make the tax-free article available for external use in medicine.

Amylum. (Southworth, Thomas S.)—While it is an established fact that even young infants are prepared to digest moderate quantities of boiled starch, the indication for its use appears to lie in those suffering from disturbances of digestion and nutrition. The chief end subserved by the addition of starch is not solely to nourish the infant, but to promote nutrition by making possible a more orderly digestion and absorption of its main nutriment, milk.—*J. Am. M. Assoc.*, 1914, vol. 63, p. 1377.

Camphor. (Cairis, Valentine.)—The comparative toxicity of camphor in different vehicles. In the undissolved state the lethal dose of camphor in the digestive system of the guinea-pig is between 0.14 and 0.18 Gm. per 100 Gm. body weight. In ether-alcohol solution the toxicity is markedly increased. Dissolved in oil, it is notably less poisonous. When given hypodermically, the toxicity of camphor in oily solutions is far below that in alcohol and water, and in all cases is greater than the effect produced by oral administration. The toxicity is much higher by peritoneal injection than by any other way of administration; but by this method the oily solution is still the least toxic of any.—*J. Pharm. Chem.*, 1914, vol. 10, p. 224; *Pharm. J.*, 1914, vol. 93, p. 457.

Cottonroot Bark.—Power and Browning report a chemical examination of cottonroot bark. No alkaloid is contained in the bark, and no evidence could be obtained of the presence of tannin.—*Pharm. J.*, 1914, vol. 93, p. 423.

Ergot. (Rosenbloom and Schildecker.)—The successful isolation of ergotin in crystals from certain organs in a case of acute ergot poisoning.—*J. Am. M. Assoc.*, 1914, vol. 63, pp. 1203, 1204.

Ipecac. (Hesse, O.)—Ipecamine and hydroipecamine, two new alkaloids, were found in the course of an investigation of the alkaloidal constituents of ipecacuanha.—*Liebig's Annalen*, 1914, vol. 403, p. 1; *Pharm. J.*, 1914, vol. 93, p. 425.

Mercuric Benzoate. (Rupp and Hermann.)—Mercuric benzoate, which is official in the French Pharmacopœia, has been recommended as the most suitable salt for hypodermic injection. Since it is a normal salt it is not apparent why it should be less ionized in solution than any other mercuric salt.—*Arch. d. Pharm.*, vol. 252, No. 3; *Pharm. J.*, 1914, vol. 93, p. 323.

The Prognosis in Morphine Addiction. (König, H.)—The prognosis naturally varies according as the addiction was acquired in connection with a chronic painful affection, such as tabes, neuralgia, or peritoneal adhesions, or with single periods of pain, such as gall-stone colic, or in connection with periods of melancholia or insomnia. Experience with 28 cases is reviewed, demonstrating a successful outcome in over 50 per cent. of the 14 in the gall-stone group. The treatment required from three to ten months in these cases.—*Berl. klin. Wchnschr.,* vol. 51, June 1, No. 22; *J. Am. M. Assoc.,* 1914, vol. 63, p. 204.

Commercial Papain and Its Assay. (Adams, H. M.)—Commercial papain is sometimes adulterated with starch or pepsin. The presence of starch is shown by the addition of iodine solution, and the pepsin by comparative observations on the digestion of meat in a weak acid and in a neutral or alkaline solution. To determine the proteolytic power of papain, neutral solutions give the most satisfactory results with either meat or the whites of eggs.—*J. Ind. and Eng. Chem.,* 1914, vol. 6, pp. 669, 670.

Acitrin.—Phenolcinchoninicacidethylester, a yellowish, odorless, and tasteless powder, melting at 59°, only slightly soluble in organic solvents. On boiling with acids or alkalies the ester is saponified.—*Südd. Apoth.-Ztg.,* 1914, vol. 54, p. 137.

Agar-agar Biscuits. (*Anon.*)—To make agar-agar biscuits it is only necessary to add the fine agar-agar to the flour used in making the biscuits. The amount should be, if possible, sufficient so that a dose (5 grammes) may be included in each biscuit.—*J. Am. M. Assoc.,* 1914, vol. 63, p. 1224.

Algocratine.—Mannich and Leemhuis report an examination of a powder offered as an infallible remedy for migraine, neuralgia, grippe, influenza, and other diseases. The preparation was found to consist essentially of a mixture of phenacetin, 50 Gm., caffeine, 10 Gm., and pyramidon, 40 Gm. The claims made for the composition of the preparation were found to be quite untrue.—*Apoth.-Ztg.,* 1914, vol. 29, p. 553.

Amphotropin.—A combination of camphoric acid and hexamethylentetramine, $C_8H_{14}(COOH)_2[(CH_2)_6N_4]_2$. A white crystalline powder having an acid reaction, soluble in 10 parts of water at room temperature, more readily soluble in hot water and in alcohol.—*Südd. Apoth.-Ztg.,* 1914, vol. 54, p. 137.

Apendicol. (Mannich and Leemhuis.)—This name is applied to a paraffin oil colored red and containing a minute quantity of fruit ether as a flavor.—*Apoth.-Ztg.*, 1914, vol. 29, p. 672.

Apyron. (*Anon.*)—Lithium acetylsalicylate. Contains 96.26 per cent. of acetyl salicylic acid and 3.74 per cent. of lithium.—*Chem.* and *Drug.*, 1914, vol. 85, p. 376.

Arsylate. (*Anon.*)—Dimethyl aminotetramido-arseno-benzene. A liquid easily absorbed in subcutaneous injection. It is a substitute for salvarsan.—*Chem.* and *Drug.*, 1914, vol. 85, p. 376.

Atrinal. (*Anon.*)—Atropine-sulphonic acid, a new mydriatic preparation manufactured by the Hoffmann-La Roche Company.—*Chem.* and *Drug.*, 1914, vol. 85, p. 376.

Catin. (Mannich and Leemhuis.)—A preparation marketed under this name was, on examination, found to consist of zinc sulphocarbonate.—*Apoth.-Ztg.*, 1914, vol. 29, p. 694.

Cerephysin.—The name applied to an extract made from the infundibular portion of the hypophyses of cattle. One cubic centimetre of cerephysin corresponds to 0.2 Gm. of moist organ substance. It occurs as a clear water-white liquid dispensed only in ampoules.—*Südd. Apoth.-Ztg.*, 1914, vol. 54, p. 137.

Chineonal. (Erdt, V.)—Fatal poisoning in a child of three who swallowed nine tablets of chineonal tablets during the day. The child had taken in the tablets the equivalent of 0.648 gramme of veronal in six or eight hours.—*Münch. med. Wchnschr.*, vol. 51, August 25, No. 34; *J. Am. M. Assoc.*, 1914, vol. 63, p. 1431.

Collargol. (Cromwell, Andrew J.)—Collargol in pyelography, with a report of an interesting case and a note on a number of experiments on dogs. From the pathologic findings and from the experimental work on dogs the author is convinced that the use of collargol in pyelography is not without danger, and that efforts should be made to secure a substance less harmful for this purpose.—*J. Am. M. Assoc.*, 1914, vol. 63, pp. 1387–1389.

Digimorval. (*Anon.*)—Each tablet is said to contain 0.005 Gm. of morphine and 0.05 Gm. of powdered digitalis and 3 drops of mentholvalerianate.—*Südd. Apoth.-Ztg.*, 1914, vol. 54, p. 153.

Friedmann Remedy.—Additional contributions on the Friedmann remedy emphasize previous reports that the remedy has not proved successful either in simple cases of tuberculosis, in surgical cases, or in lupus.—*Therap. Monatsh.*, 1914, vol. 28, p. 630.

Friedmann Remedy. (Editorial.)—In the Public Health Service report on the Friedmann remedy the investigators summarize their conclusions in the following succinct statements: "The claim of Dr. F. F. Friedmann to have originated a specific cure for tuberculosis is not substantiated by our investigation. The claim of Dr. F. F. Friedmann that the inoculation of persons and animals with his organisms is without harmful properties is disproved."—*J. Am. M. Assoc.*, 1914, vol. 63, pp. 1690, 1691.

Lacpinin. (Kühl, Hugo.)—This article was found to be an emulsion of pine needle oil containing 20 per cent. of the oil of *Abitis sibiricæ.*—*Südd. Apoth.-Ztg.*, 1914, vol. 54, p. 488.

Neohexal.—A combination of hexamethylenetetramine and sulpho-salicylic acid which has been recommended as an antiseptic for the urinary tract.—*Therap. Monatsh.*, 1914, vol. 28, p. 629.

Orthoform. (McCleave, T. C.)—Idiosyncrasy to orthoform. The experience reported indicates that it cannot be used with impunity in all persons, even in very small doses.—*J. Am. M. Assoc.*, 1914, vol. 63, p. 1666.

Parakodin.—A proprietary name for di-hydro-codeine which has been recommended as an expectorant, a sedative, and a substitute for morphine. Among the secondary effects observed are decrease in appetite, retching and nausea. It is given in doses of from 0.02 to 0.05 Gm.—*Therap. Monatsh.*, 1914, vol. 28, p. 630.

Phenoval.—A sedative and hypnotic which has been recommended for the reduction of pain and for nervous patients; also as a narcotic. —*Therap. Monatsh.*, 1914, vol. 28, p. 629.

Rhodoform. (*Anon.*)—A sulphocyanate of hexamethylene-tetramine. It is a white, odorless powder, recommended as an antiseptic for use in the treatment of diseases of the mouth and larynx.—*Chem.* and *Drug.*, 1914, vol. 85, p. 376.

Thiophysein. (*Anon.*)—A new organic iodine preparation, being an addition-product of ethyl-thio-urea and ethyl iodide. It is easily soluble in water, and is, therefore, a suitable form for the administration of iodine in organic combination.—*Chem.* and *Drug.*, 1914, vol. 85, p. 376.

CURRENT LITERATURE.

Digitalis.

The second instalment of Dr. Robert H. Hatcher's two-part paper on digitalis is presented in the October number of the *Druggists Circular,* and, like its precursor, is both interesting and instructive. In it he deals altogether with the pharmacology of this much-experimented-with and much-discussed drug, and closes with an excellent summary which embraces the conclusions arrived at in both papers. An adequate abstract of these papers is almost impossible. Physicians and pharmacists should really read and study the original papers.

The author recapitulates as follows: "Digitalis of the first year's growth is probably as active as that of the second, the cultivated as active as the wild-grown.

"The most active digitalis is not necessarily the best; the best being that which possesses a maximum of therapeutic actions with a minimum of side actions, such as the nauseant and emetic. It is not known at what period digitalis possesses this advantage.

"The drying and storage of digitalis require no exceptional conditions. Like all vegetable drugs, it should be selected carefully, dried properly, and stored so that it will not become mouldy. It will then keep indefinitely.

"Pharmaceutical preparations of digitalis which contain at least 60 per cent. of alcohol in the finished product will keep almost indefinitely under all ordinary conditions of storage, where the containers are kept securely corked and away from sunlight.

"At least two principles—digitoxin (or crystalline digitalin of Nativelle), and true digitalin of Schmiedeberg, or of Kiliani—are obtained from digitalis leaf, and it is possible that a third therapeutically active substance, digitalein, may be so obtained in *fairly* pure form, but not *absolutely* pure.

"It is not absolutely certain that these exist preformed in the leaf.

"There is no digitalis principle or preparation, pharmacopœial or proprietary, which has the advantage of digitalis without certain undesired effects, such as nausea and vomiting. Cumulation, so-called, also pertains to all digitalis principles, as, indeed, it does to all drugs.

"Any pharmacist can obtain digitalis without paying an exorbitant price for it, and he can make a tincture equal to the best, and quite as useful therapeutically as any of the proprietary preparations.

"The tincture represents all of the activities of the leaf; so does the infusion when properly made from leaf in No. 60 powder, and these two preparations have an identical action in corresponding doses.

"The fat-free tincture has no advantages over the official tincture.

"The determination of the digitoxin content of the leaf affords no index of the therapeutic or pharmacologic activity of the drug, but the therapeutic activity may vary in the same direction as the digitoxin.

"No test for digitalis, chemical or biologic, is satisfactory, but the one-hour frog method is probably best suited to the general needs of the pharmacist, and this will probably be admitted to the ninth edition of the United States Pharmacopœia.

"The dose of digitalis cannot be expressed in fixed terms, because it varies widely with the frequency of repetition, the length of time during which it is intended to be taken, and dependent upon whether the patient has recently had similar medication. It is probably safe to say that not more than 45 grains of the leaf or a fluidounce of the tincture should be administered to a patient within a period of one week, and such an amount only under the immediate observation of a trained clinician, and such an amount could not be given safely immediately after medication with digitalis or synergistic drugs." *The Druggists Circular,* October, 1914, p. 607.

J. K. T.

NEWS ITEM

Dr. Frederick B. Power will retire from the directorship of the Wellcome Chemical Research Laboratories on the first of December in order to return to the United States where, for family reasons, he will make his future home, at 535 Warren Street, Hudson, New York.

The high character of the research work carried out in these Laboratories under the immediate direction of Dr. Power stands without a parallel in his department of science. It has been truly said that Dr. Power has, during the period of his administration, inaugurated a new era in his field of research in England.

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TO VOLUME 86 OF THE AMERICAN JOURNAL OF PHARMACY.[1]

AUTHORS.

[1] Compiled by M. G. Smith.

SUBJECTS

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The College was organized with the twofold purpose of providing a system of instruction in Pharmacy and subjecting Apothecaries to regulations in their business. Throughout ninety-two years the College has been conducted with the purpose of its founders foremost in the minds of its Officers and Trustees.

The College is not an association of stockholders, it being conducted by Members, who pay annual dues and who annually elect a Board of Trustees, which Board is the executive body of the institution. Membership in the College is limited to reputable persons interested in Pharmacy or an allied science.

Any surplus in the annual income of the College is applied to the further perfection of the facilities of the College.

The College has always been, and is at present, conducted by men intimately connected with the retail drug business.

World-Wide Protest Against Fraudulent Advertising

¶ Honest business men the world over are raising a protest against the practice of deceiving the public by false advertising. The resolution introduced in the International Congress of Chambers of Commerce in Paris by a delegate from Temesvar, Hungary, might have been drafted in America, it describes practices here so well. The delegate asked the Congress to call on the Parliaments of the world to make laws forbidding the publication of fraudulent advertisements, against the wrongful use of exhibition awards, against false statements of the origin of goods and against misleading names and prices and quantities.

¶ Some progress toward bringing about these much-needed reforms has been made in the United States, but there is still room for improvement. The reputable business man is as deeply interested in penalizing dishonest methods as is the consumer; the business man has to meet fraudulent competition and all business suffers in consequence. But the frauds continue, and it is impossible for the society of business men right here in Philadelphia to prevent all of them at home. It should be made as perilous for a man to take money out of a customer's pocket by false advertising as to put his hand into the customer's purse and filch his coin.

—Editorial in Public Ledger, Philadelphia